

# Prospective Study of the Effect of the 21-Gene Assay on Adjuvant Clinical Decision-Making in Japanese Women With Estrogen Receptor-Positive, Node-Negative, and Node-Positive Breast Cancer

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## Abstract

**In a prospective study in 124 Japanese women with estrogen receptor-positive (ER+) invasive early breast cancer (EBC), the effect of the 21-gene assay on adjuvant decision-making was examined. Overall, treatment recommendations changed in 33% (95% confidence interval [CI], 24%-43%) of node-negative (N0) and 65% (95% CI, 41%-85%) of node-positive (N+) patients, predominantly from chemohormonal to hormonal therapy. Results from this Japanese population confirm US and European experiences.**

**Background:** In this study we investigated if the 21-gene assay result affects adjuvant decision-making in Japanese women with ER+ invasive EBC. **Patients and Methods:** A total of 124 consecutive eligible patients with ER+, HER2-negative EBC and 0 to 3 positive lymph nodes were enrolled. Treatment recommendations, physicians' confidence and patients' decisional conflict before and after knowledge of the Recurrence Score results of the 21-gene assay were recorded.

**Results:** One-hundred four patients (84%) had N0 disease, including micrometastases, and 20 (16%) had N+ disease. Overall, recommendations changed in 33% (95% CI, 24%-43%) of N0 and 65% (95% CI, 41%-85%) of N+ patients. In 27 of 48 (56%) of N0 and 13 of 15 (87%) of N+ patients an initial recommendation for chemohormonal therapy was revised to only hormonal therapy after assay results, and in 7 of 56 (13%) of N0 and 0 of 5 N+ patients from only hormonal to combined chemohormonal therapy. Decisions appeared to follow the Recurrence Score results for low and high values. For patients with intermediate Recurrence Score values, overall recommendations for chemohormonal treatment tended to decrease after assay results. Physicians' confidence increased in 106 of 124 (85.5%; 95% CI, 78%-91%) cases. Patients' decisional conflict significantly improved as indicated by changes in the total score and the 5 defined subscores ( $P = .014$  for Informed Subscore;  $P < .001$  for all others). **Conclusion:** Results from this prospective study in a Japanese population confirm an effect of the 21-gene assay results on adjuvant treatment decision-making, consistent with reported experiences from the United States and Europe.

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**Keywords:** Adjuvant, Chemotherapy, Early breast cancer, Multi-gene assay, Recurrence Score

## Introduction

The incidence of breast cancer is still increasing in Japan.<sup>1</sup> Although breast cancer mortality rates in Western countries are

decreasing, they are still increasing in Japan.<sup>2</sup> Preventing future distant recurrences is the crucial primary objective of adjuvant therapy. Hormone receptor-positive disease accounts for roughly

Submitted: Jun 29, 2013; Revised: Oct 1, 2013; Accepted: Oct 23, 2013; Epub: Oct 26, 2013

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## Twenty-one—Gene Assay in Japanese Breast Cancer Patients

75% of Japanese breast cancer cases.<sup>3</sup> Routinely, such patients receive adjuvant hormonal treatment. Many of these patients are also treated with adjuvant chemotherapy although a substantial proportion will not derive any clinical benefit in terms of a further reduction of their risk of recurrence.<sup>4</sup> Recently, the traditional instrumentarium of clinical and histopathological prognostic markers has been complemented by genomic markers such as the multigene 21-gene Recurrence Score assay.

The 21-gene assay measures the mRNA expression of 16 cancer-related and 5 reference genes selected based on correlation of gene expression and risk of distant recurrence in 3 development studies.<sup>5-7</sup> The assay is based on reverse transcription polymerase chain reaction, which was specifically optimized to be used in archival formalin-fixed, paraffin-embedded tumor tissue,<sup>8,9</sup> and can thus be performed on routinely processed and archived tumor blocks or slides. Using an algorithm based on the results of clinical studies, the Recurrence Score result—a numeric score between 0 and 100—is calculated.<sup>10</sup> The score is a continuous variable quantifying the risk of distant recurrence at 10 years for the individual patient<sup>10</sup> with estrogen receptor-positive (ER+) early breast cancer treated with adjuvant hormonal therapy. A lower Recurrence Score value corresponds to a lower risk of recurrence, and a higher value corresponds to a higher risk of recurrence. Three risk categories have been defined: low, intermediate, and high risk groups for Recurrence Score values < 18, 18 to 30, and  $\geq 31$ , respectively.<sup>10</sup> The prognostic significance of the 21-gene assay for node-negative (N0) and node-positive (N+) disease has been validated using tumor specimens from patients with ER+ early breast cancer enrolled prospectively in large randomized phase III studies.<sup>4,10-12</sup> Furthermore, the assay was shown to be predictive of the benefit of chemotherapy in N0 and N+ ER+ patients.<sup>4,12</sup> Patients with tumors that had a high Recurrence Score result had the largest proportional benefit of chemotherapy, and those presenting with a tumor with a score < 18, did not appear to benefit from chemotherapy.

The 21-gene assay has been included in guidelines of scientific societies such as American Society of Clinical Oncology,<sup>13</sup> National Comprehensive Cancer Network (NCCN),<sup>14</sup> and European Society for Medical Oncology.<sup>15</sup> The updated 2011 St Gallen Consensus Panel acknowledges the test as the only multiparameter gene assay considered useful, not only as a prognostic test, but also as a marker predictive of chemotherapy responsiveness in hormone receptor-positive early breast cancer where uncertainty remains after consideration of other tests.<sup>16</sup>

Several clinical utility studies have demonstrated that knowledge of Recurrence Score results affects management of patients. Results of these retrospective and prospective studies are very consistent for N0 ER+ disease and show a revision of treatment recommendations in approximately 35% of cases as reported in a recent metaanalysis.<sup>17</sup> Recommendations shift predominantly from adjuvant chemohormonal treatment to hormonal treatment alone. The database for N+ disease is still evolving.<sup>18,19</sup> Results suggest a similar effect for patients with 1 to 3 positive lymph nodes.

It was also shown that the 21-gene assay was applicable to adjuvant therapy decision-making beyond the largely Caucasian populations in which it was originally validated. A recently published confirmatory study demonstrated that the assay provided prognostic information in

a population of Japanese women with ER+ N0 early breast cancer treated with adjuvant tamoxifen.<sup>2</sup> Notably, the authors reported that the expression profiles of individual genes and gene groups for the Japanese patients were very similar to those for the patients from the validation study National Surgical Adjuvant Breast and Bowel Project B-14: A Clinical trial to assess Tamoxifen in patients with primary breast cancer and negative axillary nodes whose tumors are positive for estrogen receptors with confidence intervals for the hazard ratios for distant recurrence for the 2 studies overlapping for all genes and gene groups. Physicians in Japan have started to use the assay as a tool in routine adjuvant decision-making. Japanese guidelines describe the assay as an option for consideration to aid decisions on whether chemotherapy should be used for hormone receptor-positive breast cancer in the adjuvant setting.<sup>20</sup> However, thus far, no prospective clinical utility data of the 21-gene assay have been generated in a population of women in Japan. Thus, we conducted a clinical study to analyze the influence of Recurrence Score information on the adjuvant decision-making process in Japanese patients with ER+ N0 or N+ early-stage breast cancer.

## Patients and Methods

This was a prospective, multicenter study performed in 2 Japanese centers. The study was approved by the respective institutional ethics committees. All patients provided written informed consent.

### Study Objectives

The primary study objective was to characterize the degree to which Recurrence Score results affect physician recommendations for adjuvant therapy and physicians' expressed level of confidence in the recommended treatment plan in a cohort of consecutive patients with ER+, HER2-negative breast cancer with up to 3 positive lymph nodes.

A secondary study objective was to assess the effect of assay results on patients' level of decisional conflict. An additional secondary objective was to provide a basis for indirect estimates of net cost effects and savings from a Japanese societal perspective that might result from using the assay. This health economic assessment is beyond the scope of the current report.

### Patients

Enrollment was offered consecutively to eligible women who had operable ER+, HER2-negative breast cancer, either with N0 (pre- and postmenopausal patients) or micrometastatic disease (postmenopausal patients) or with histologically verified lymph node metastases in 1 to 3 lymph nodes (postmenopausal patients only). Patients had to be 18 years of age or older with adequate performance status to be candidates for systemic chemotherapy, and to be able to give consent and answer written questions in Japanese. To participate in the study, patients were required to incur the costs of the assay as an out-of-pocket expense.

### Physicians

Seventeen physicians participated in the study. They had to be either medical oncologists or surgeons making adjuvant treatment recommendations to breast cancer patients. At least 1 physician of a participating center needed to have previously ordered the 21-gene assay.

### Physician Questionnaires

A baseline questionnaire developed for use in this study on the basis of a published questionnaire<sup>21</sup> captured physicians' initial treatment recommendations, largely based on effective Japanese<sup>20</sup> and NCCN guidelines,<sup>14</sup> and answers to queries regarding their confidence in their treatment recommendations before the assay was performed. A follow-up questionnaire recorded physicians' treatment recommendations and confidence in their recommendations after knowledge of the assay results. For the latter, physicians responded to the statement "I am more confident in my treatment recommendation after ordering the assay" according to a Likert scale with the options: "strongly disagree," "disagree," "neither disagree nor agree," "agree," "strongly agree," and "do not know."

### Patient Questionnaires and Decisional Conflict Scale

At baseline and after results of the assay were discussed, patients completed the 16-item Decisional Conflict Scale (DCS). This scale has been validated to assess patient perceptions of uncertainty in making decisions about health care treatment options and satisfaction with treatment decision-making.<sup>22,23</sup> Regarding the DCS, the test-retest (2 weeks later) reliability coefficient was 0.81. Internal consistency coefficients ranged from 0.78 to 0.92.

The DCS has a Total Score and 5 subscores: the Informed, Values Clarity, Support, and Uncertainty Subscores are based on 3 items each and the Effective Decision Subscore is based on the remaining 4 items.

### Statistical Methods

The proportion of patients whose treatment recommendations changed from baseline to follow-up was calculated along with the respective 95% confidence interval (CI) using the Clopper-Pearson method. McNemar's test was used to assess whether the proportion of patients who were initially recommended chemotherapy was

changed after the 21-gene assay. These analyses were conducted separately according to nodal status (N0, including micrometastases [N1mic], vs. N+), and combined. The proportion of cases in which the physician either agreed or strongly agreed that they were more confident in their treatment recommendation after the assay was calculated along with the respective 95% CI.

The DCS data from the baseline and follow-up questionnaires were analyzed similarly. Each of the 5 subscores was calculated as the sum of the component items only if there were responses to each of the defined items, and transformed to a range from 0 to 100 with smaller scores reflecting less decisional conflict. If any subscore was missing, the Total Score was set to missing. If all 5 subscores were not missing, then the Total Score was calculated as:

Total Score =  $(3 \times [\text{Informed Subscore}] + 3 \times [\text{Values Clarity Subscore}] + 3 \times [\text{Support Subscore}] + 3 \times [\text{Uncertainty Subscore}] + 4 \times [\text{Effective Decision Subscore}]) / 16$ . The changes from baseline to follow-up in the DCS Total Score and each of the subscores were analyzed using paired-sample *t* tests.

The study was designed to enroll 200 patients, with the original intent to estimate a decision change rate of 20% with a precision of  $\pm 5\%$  to 6%. However, it was decided to halt enrollment after 124 patients were enrolled because the accumulating data indicated that there were statistically significant reductions in treatment recommendations for chemotherapy in N0 and N+ patient subgroups.

## Results

### Patient and Tumor Characteristics

One-hundred twenty-four patients were enrolled between July 2009 and June 2011. Complete patient and tumor characteristics and the distribution of Recurrence Score values are listed in Table 1. In the N0 subset, 50 (48%) patients had a low score < 18, 37 (36%) had an intermediate score of 18 to 30, and 17 (16%) had a high

**Table 1** Patient Characteristics

Characteristic	All (n = 124)	N0 (n = 104)	N+ (1-3 Positive Nodes) (n = 20)
<b>Mean Age</b>			
Years	51.4	49.8	59.9
<b>Tumor Size</b>			
≤2 cm	76 (61.3)	63 (60.6)	13 (65.0)
>2 cm	48 (38.7)	41 (39.4)	7 (35.0)
<b>Tumor Grade</b>			
Well	44 (35.5)	31 (29.8)	13 (65.0)
Moderate	35 (28.2)	30 (28.8)	5 (25.0)
Poor	45 (36.3)	43 (41.3)	2 (10.0)
<b>Menopausal Status</b>			
Premenopausal	62 (50.0)	62 (59.6)	0 (0.0)
Postmenopausal	62 (50.0)	42 (40.4)	20 (100.0)
<b>Recurrence Score Values</b>			
Low	62 (50.0)	50 (48.1)	12 (60.0)
Intermediate	44 (35.5)	37 (35.6)	7 (35.0)
High	18 (14.5)	17 (16.3)	1 (5.0)

Data are reported as n (%) except where otherwise noted.  
Abbreviations: N0 = node-negative; N+ = node-positive.

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**Table 2** Chemotherapy Recommendations Before and After Assay Overall and According to Nodal Status

	After Assay		
	HT	CHT	All
<b>All Evaluable Patients</b>			
Before Assay			
HT	54 (44%)	7 (6%)	61 (49%)
CHT	40 (32%)	23 (19%)	63 (51%)
All	94 (76%)	30 (24%)	124
<b>Node-Negative Patients</b>			
Before Assay			
HT	49 (47%)	7 (7%)	56 (54%)
CHT	27 (26%)	21 (20%)	48 (46%)
All	76 (73%)	28 (27%)	104
<b>Node-Positive Patients</b>			
Before Assay			
HT	5 (25%)	0 (0%)	5 (25%)
CHT	13 (65%)	2 (10%)	15 (75%)
All	18 (90%)	2 (10%)	20

McNemar's test exact  $P < .001$ .

Abbreviations: CHT = chemohormonal therapy; HT = hormonal therapy.

score of  $\geq 31$ . Distribution of patients in the smaller N+ subset according to risk group was 12 (60%) patients with low, 7 (35%) with intermediate, and 1 (5%) with high Recurrence Score values.

### Treatment Recommendations Before and After Knowledge of Recurrence Score Result

Treatment recommendations before and after the 21-gene assay are listed in Table 2. Initial treatment recommendations were revised in 47 of 124 (38%; 95% CI, 29%-47%) of all patients, 34 of 104 (33%; 95% CI, 24%-43%) of patients with N0 and 13 of 20 (65%; 95% CI, 41%-85%) of patients with N+ disease after knowledge of the Recurrence Score results.

For all patients recommended chemohormonal therapy (CHT) before the assay, treatment recommendations were revised to hormonal therapy (HT) only in 40 of 63 (63%; 95% CI, 50%-75%) total patients, including 27 of 48 (56%; 95% CI, 41%-71%) with N0 disease, and 13 of 15 (87%; 95% CI, 60%-98%) with N+ disease. For all patients initially recommended HT alone, the recommendations after assay changed to CHT in 7 of 61 (11%; 95% CI, 5%-22%) total patients, all 7 of whom were from those 56 patients with N0 disease (13%; 95% CI, 5%-24%).

Overall, the shift in treatment recommendations was predominantly from CHT to HT ( $P < .001$  for N0 patients and  $P < .001$  for N+ patients by McNemar's test), ultimately resulting in a net reduction of adjuvant chemotherapy (Table 2 and Fig. 1). All patients in the low Recurrence Score group were recommended HT and, similarly, 100% of patients in the high Recurrence Score group were recommended CHT, indicating that for N0 and N+ patients, treatment recommendations after assay appeared to directly follow the low and high Recurrence Score categorizations (Fig. 1). For patients with intermediate Recurrence Score values, in N0 patients recommendations for CHT decreased by an absolute 19%, and in N+ patients by an absolute of 86% after the assay (Table 3).

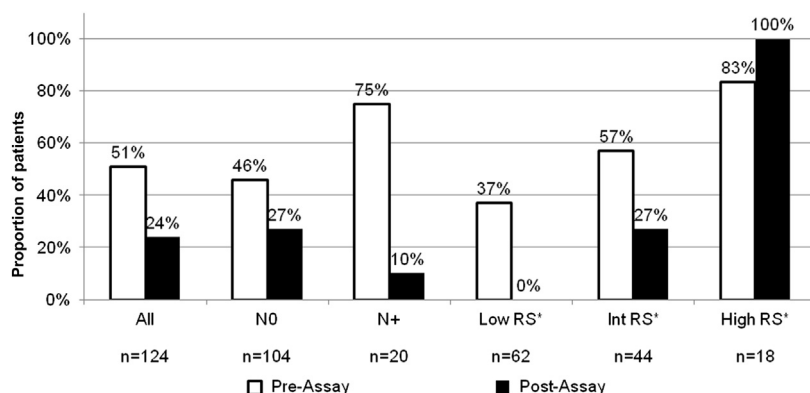
### Physicians' Confidence in Treatment Recommendation

Physicians either agreed or strongly agreed that they were more confident in their treatment recommendations after the assay in 106 of 124 (85%; 95% CI, 78%-91%) cases. Physicians disagreed in 7% of cases and neither agreed nor disagreed in 8% of cases (Fig. 2).

### Patients' Decisional Conflict Before and After the 21-Gene Assay

The Total Score of the Decisional Conflict Scale before and after assay was available for 116 patients. The mean values of the 5 subscores and the Total Score are listed in Table 4. Each of the 5 subscores and the Total Score decreased significantly ( $P = .014$

**Figure 1** Recommendation for Adjuvant Chemotherapy Pre- and Post-Assay



Abbreviation: RS = Recurrence Score result.

\*Regardless of nodal status.

**Table 3** Changes in Treatment Recommendations

Patients	n	Overall Change Rate, Before to After Assay	CHT to HT	HT to CHT	No Change	CHT to CHT	HT to HT
<b>All Evaluable</b>	124	47 (38%; 95% CI, 29%-47%)	40 (32%)	7 (6%)	77 (62%)	23 (19%)	54 (44%)
Low RS	62	23 (37%)	23 (37%)	0 (0%)	39 (63%)	0 (0%)	39 (63%)
Intermediate RS	44	21 (48%)	17 (39%)	4 (9%)	23 (52%)	8 (18%)	15 (34%)
High RS	18	3 (17%)	0 (0%)	3 (17%)	15 (83%)	15 (83%)	0 (0%)
<b>Node-Negative</b>	104	34 (33%; 95% CI, 24%-43%)	27 (26%)	7 (7%)	70 (67%)	21 (20%)	49 (47%)
Low RS	50	16 (32%)	16 (32%)	0 (0%)	34 (68%)	0 (0%)	34 (68%)
Intermediate RS	37	15 (41%)	11 (30%)	4 (11%)	22 (59%)	7 (19%)	15 (41%)
High RS	17	3 (18%)	0 (0%)	3 (18%)	14 (82%)	14 (82%)	0 (0%)
<b>Node-Positive</b>	20	13 (65%; 95% CI, 41%-85%)	13 (65%)	0 (0%)	7 (35%)	2 (10%)	5 (25%)
Low RS	12	7 (58%)	7 (58%)	0 (0%)	5 (42%)	0 (0%)	5 (42%)
Intermediate RS	7	6 (86%)	6 (86%)	0 (0%)	1 (14%)	1 (14%)	0 (0%)
High RS	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)	0 (0%)

95% Confidence intervals calculated using the Clopper-Pearson method.

Abbreviations: CHT = chemohormonal therapy; HT = hormonal therapy; RS = Recurrence Score result.

for Informed Subscore;  $P < .001$  for all others), indicating an overall reduction in patients' decisional conflict after knowledge of the Recurrence Score result. The mean Total Score improved by 26% after patients received the assay results.

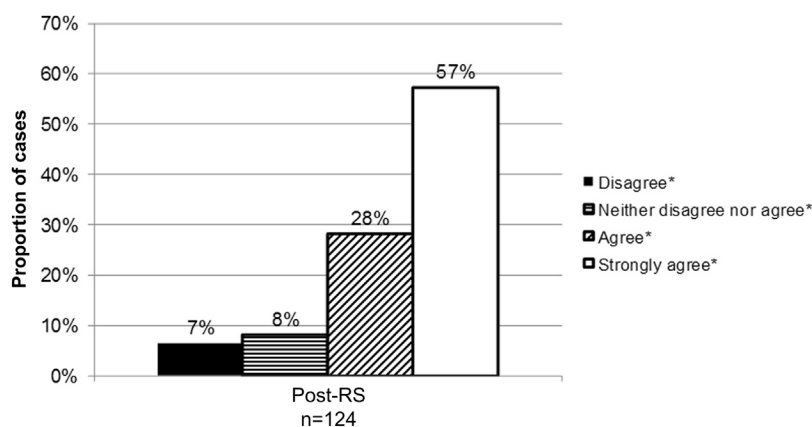
## Discussion

This is the first study of the effect of the 21-gene assay on clinical decision-making in early invasive breast cancer in an Asian patient population. Moreover, our study is one of the first decision impact studies for the assay that includes N0 and N+ patients.

Regarding N0 disease, the results of our study are consistent with those reported from other prospective decision impact studies from the United States,<sup>21</sup> Spain,<sup>24</sup> and Germany.<sup>19</sup> Overall change rates in these prospective studies ranged from 30% to 32%. The metaanalysis of 9 studies and 1154 patients reported a change rate of 35%.<sup>17</sup> We found an overall change rate of 33%. Change rates

in the United Kingdom<sup>25</sup> and Australia<sup>18</sup> were somewhat lower with 27% and 24%, perhaps in part because the proportion of patients with an initial recommendation for chemotherapy in these studies was much lower (40% and 24%, respectively), than in our study (51%) and the other 3 cited. However, regardless of baseline tendencies to use either more conservative or aggressive treatment approaches across all studies to date, decision changes attributable to the 21-gene assay appear to occur in both directions—foregoing chemotherapy in many patients, and adding it in others.

Regarding N+ disease, results vary among other studies of the effect of Recurrence Score results in N+ early breast cancer patients. A retrospective study in 135 patients with ER+ disease including 9 patients with N1mic and 11 patients with N+ disease found an overall change rate in treatment recommendations of 25%. The authors found no correlation of therapy change and

**Figure 2** Change in Physicians' Confidence After The 21-Gene Assay

Abbreviation: RS = Recurrence Score result.

\*Answers to the question (post-RS): "I am more confident in my treatment recommendation."



**Table 4** Changes From Before Assay to After Assay in Decisional Conflict

Score	n <sup>a</sup>	Pre-RS Mean	Post-RS Mean	Mean Change (95% CI)	P <sup>b</sup>
Informed Subscore	121	26.2	22.1	4.1 (0.9-7.4)	.014
Values Clarity Subscore	122	28.6	22.3	6.2 (2.9-9.5)	<.001
Support Subscore	120	22.6	17.6	5.0 (2.2-7.8)	<.001
Uncertainty Subscore	121	44.6	30.5	14.0 (9.0-19.1)	<.001
Effective Decision Subscore	122	24.3	17.7	6.6 (3.9-9.2)	<.001
Total Score	116	28.8	21.4	7.4 (4.7-10.0)	<.001

Abbreviation: RS = Recurrence Score result.

<sup>a</sup>Number of patients for whom all items were not missing for the pre-assay and the post-assay questionnaires.

<sup>b</sup>P value from paired *t* test.

nodal stage.<sup>26</sup> A US Web-based retrospective physician survey reported a change rate of 51% in 138 N+ ER+ patients with a change from CHT to HT in 33%.<sup>27</sup> In the Australian study,<sup>18</sup> the Recurrence Score result led to a 26% change in treatment recommendations in 50 patients with 1 to 3 positive lymph nodes: 12 patients changed to HT and 1 to CHT. In the German study there was a 39% change rate in 122 patients, with a predominant change from CHT to HT in 28% of all N+ cases and a 37% change among the 92 N+ patients with an initial recommendation for CHT.<sup>19</sup> In this study, we saw a 65% (95% CI, 41%-85%) shift in treatment recommendations in the 20 N+ patients, with all changes made from CHT to HT. These patients all had low and intermediate Recurrence Score values. It should be noted that we only offered the test to N+ patients who were postmenopausal, in accordance with the validation study in N+ disease.<sup>12</sup> This was not a prerequisite in the other studies cited. Thus, physicians in our study might more readily have omitted chemotherapy. Furthermore, because all patients were required to pay out-of-pocket for the cost of the assay, the study might have preselected patients who were more inclined and generally more confident to forego chemotherapy from the outset. The small number of patients with N+ disease in our study is a major limitation to drawing more general conclusions, and further studies might be warranted to better define the effect of the assay when offered to N+ patients.

Generally, for patients in the low and in the high Recurrence Score groups, treatment recommendations after assay corresponded completely with the Recurrence Score results in our study. The US, Spanish, and German studies have similarly observed that the shifts in treatment recommendations followed the Recurrence Score values. However, although all patients with high Recurrence Score results were recommended chemotherapy in these studies, a small minority of patients in the low Recurrence Score groups remained with recommendations for chemotherapy despite Recurrence Score values < 18. For physicians in our study, the assay appeared to be the final decisive parameter after consideration of all other factors. One explanation might be that patients might have been more motivated to avoid chemotherapy, particularly if their scores were low, because they paid out-of-pocket for the assay in this study.

For patients in this study with intermediate Recurrence Score results, the physicians appeared to have taken the continuous nature of the score into account, because the tendency to change from CHT to HT was greater for patients with low-intermediate scores between 18 and 25 compared with those with high-intermediate scores from 26 to 30. It should also be noted that the assay was

not offered to patients in whom a clear decision for the type of adjuvant therapy had already been made.

Similar to other studies, we found that physicians' confidence in their treatment recommendation increased in 85% of cases. In comparison, changes in physician confidence levels were 76% in the US study,<sup>21</sup> 60% in the Spanish study,<sup>24</sup> 46% in the Australian study,<sup>28</sup> and 45% in the German study.<sup>19</sup> Although all decision impact studies report sizable increases in physician confidence after receipt of Recurrence Score information, the wide range of improvements in physician confidence might reflect differences in baseline experience with use of the 21-gene assay among physician investigators in each study.

In our assessment of patients' decisional conflict, we found each of the 5 subscores and the Total Score to improve significantly, indicating overall reduction in patients' decisional conflict with knowledge of the Recurrence Score results. The mean total Decisional Conflict Score improved by 26% after knowledge of the Recurrence Score results. The analysis of the Decisional Conflict Scale in the US study<sup>21</sup> was conducted on the raw Total Scores. Applying the scaling rules used in our study to enable comparison, the mean Total Score decreased from 24.8 to 17.3, a reduction of 7.5 units, which is comparable with the mean reduction of 7.4 units seen in our study.

## Conclusion

The results from this Japanese population confirm an effect of the 21-gene assay on adjuvant treatment decision-making, consistent with studies in predominantly Caucasian populations in North America and Europe. Moreover, results indicate that the Recurrence Score values were adopted as a critical tool in adjuvant decision-making in ER+ early breast cancer in centers with previous experience with the assay. The use of the assay ultimately resulted in a net reduction in treatment recommendations for adjuvant chemotherapy. The effect on the Japanese health care system should be assessed systematically. In another article we report on health economic analyses assessing the cost-effectiveness of an adjuvant decision-making process guided by the 21-gene assay for the Japanese health care system.

## Clinical Practice Points

- The 21-gene assay was shown to be of prognostic significance and to be predictive of the benefit of chemotherapy in patients with estrogen receptor positive early breast cancer in both node-negative and node-positive disease.

- A confirmatory study in a population of Japanese women with ER+ node-negative early breast cancer treated with adjuvant tamoxifen demonstrated that it also provided prognostic information beyond the largely Caucasian populations it was originally validated in.
- The 21-gene assay has been included in guidelines of major scientific societies.
- Several clinical utility studies have demonstrated that knowledge of Recurrence Score results affects management of patients.
- In node-negative ER-positive disease results consistently show a revision of treatment recommendations in approximately 35% of cases and a predominant shift of recommendations from adjuvant chemohormonal treatment to hormonal treatment alone.
- Similar effects have been described for patients with 1 to 3 positive lymph nodes.
- The results of this prospective study in a Japanese population confirm an impact of the 21-gene assay on adjuvant treatment decision-making, consistent with studies in predominantly Caucasian populations in North America and Europe.
- The use of the assay ultimately resulted in a net reduction in treatment recommendations for adjuvant chemotherapy as well as an increase in physicians' confidence and an improvement in patients' decisional conflict.
- The data may contribute to a wider adoption of the 21-gene assay as a critical tool in adjuvant decision-making in ER+ early breast cancer in Japanese clinical practice.

## Disclosure

Dr Yamauchi has received honoraria from SRL Inc. Ms Nakagawa, Dr Hell, and Dr Nakamura serve as consultants for Genomic Health, Inc. Dr Chao and Dr Yoshizawa are employees of Genomic Health, Inc. All other authors state that they have no conflicts of interest.

## References

1. Kono A, Misumi J. The time trend of breast cancer mortality in Japan. *Arch Gynecol Obstet* 2005; 272:187-90.
2. Toi M, Iwata H, Yamanaka T, et al. Clinical significance of the 21-gene signature (Oncotype DX) in hormone receptor-positive early stage primary breast cancer in the Japanese population. *Cancer* 2010; 116:3112-8.
3. The Japanese Breast Cancer Society. Available at: <http://www.jbcs.gr.jp>. Accessed: September 25, 2013.
4. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006; 24:3726-34.
5. Esteban J, Baker J, Cronin M, et al. Tumor gene expression and prognosis in breast cancer: multi-gene RT-PCR assay of paraffin-embedded tissue. *Prog Proc Am Soc Clin Oncol* 2003; 22:850 (abstract 3416).
6. Cobleigh MA, Tabesh B, Bitterman P, et al. Tumor gene expression and prognosis in breast cancer patients with 10 or more positive lymph nodes. *Clin Cancer Res* 2005; 11:8623-31.
7. Paik S, Shak S, Tang G, et al. Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14. *Breast Cancer Res Treat* 2003; 82: abstract 16.
8. Cronin M, Pho M, Dutta D, et al. Measurement of gene expression in archival paraffin-embedded tissues. *Am J Pathol* 2004; 164:35-42.
9. Cronin M, Sangli C, Liu ML, et al. Analytical validation of the Oncotype DX Genomic Diagnostic Test for recurrence prognosis and therapeutic response prediction in node-negative, estrogen receptor-positive breast cancer. *Clin Chem* 2007; 53:1084-91.
10. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node negative breast cancer. *N Engl J Med* 2004; 351: 2817-26.
11. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol* 2010; 28:1829-34.
12. Albain K, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol* 2010; 11:55-65.
13. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2007; 25:5287-312.
14. National Comprehensive Cancer Network. Practice Guidelines in Oncology. Breast Cancer (version v3.2013). Available at: <http://www.NCCN.org>. Accessed September 25, 2013.
15. Senkus E, Kyriakides S, Penault-Llorca F, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; 24(suppl 6):vi7-23.
16. Goldhirsch A, Wood C, Coates AS. Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol* 2011; 22:1736-47.
17. Hornberger J, Chien R. Meta-analysis of the decision impact of the 21-gene breast cancer Recurrence Score in clinical practice. Poster presented at: St Gallen International Breast Cancer Conference, March 16-14, 2011; St Gallen, Switzerland.
18. de Boer RH, Baker C, Speakman D, Chao CY, Yoshizawa C, Mann GB. The impact of a genomic assay (Oncotype DX) on adjuvant treatment recommendations in early breast cancer. *Med J Aust* 2013; 199:205-8.
19. Eiermann W, Rezai M, Kümmel S, et al. The 21-gene recurrence score assay impacts adjuvant therapy recommendations for ER-positive, node-negative and node-positive early breast cancer resulting in a risk-adapted change in chemotherapy use. *Ann Oncol* 2013; 24:618-24.
20. Kanehara, et al. Breast Cancer Guideline of the Japanese Breast Cancer Society, version 2011.
21. Lo S, Mumby P, Norton J, et al. Prospective multicenter study of the impact of the 21-Gene Recurrence Score Assay on medical oncologist and patient adjuvant breast cancer treatment selection. *J Clin Oncol* 2010; 28:1671-6.
22. O'Connor AM. Validation of a decisional conflict scale. *Med Dec Making* 1995; 15:25-30.
23. O'Connor AM. User Manual — Decisional Conflict Scale. 1993 (updated 2010)). Available at: [http://decisionaid.ohri.ca/docs/develop/User\\_Manuals/UM\\_Decisional\\_Conflict.pdf](http://decisionaid.ohri.ca/docs/develop/User_Manuals/UM_Decisional_Conflict.pdf). Accessed April 2, 2009.
24. Albanell J, Gonzales A, Ruiz-Borrego M, et al. Prospective transGEICAM study of Oncotype DX in clinical decision making in women with estrogen receptor-positive, node-negative breast cancer. *Ann Oncol* 2012; 23:625-31.
25. Holt SD, Durrani S, Pudney D, et al. Results from a prospective clinical study on the impact of Oncotype DX on adjuvant treatment decision in a cohort of 142 UK patients. Abstracts of the 34th Annual CTREC-AACR San Antonio Breast Cancer Symposium, December 6-10, 2011. *Cancer Res* 2011; 71(suppl 3): abstract P5-14-26.
26. Geffen DB, Abu-Ghanem S, Sion-Vardy N, et al. The impact of the 21-gene recurrence score assay on decision making about adjuvant chemotherapy in early-stage estrogen-receptor-positive breast cancer in an oncology practice with a unified treatment policy. *Ann Oncol* 2011; 22:2381-6.
27. Oratz R, Kim B, Chao C, et al. Physician survey of the effect of the 21-gene recurrence score assay results on treatment recommendations for patients with lymph node-positive, estrogen receptor-positive breast cancer. *J Oncol Pract* 2011; 7:94-9.
28. De Boer RH, Baker C, Speakman, et al. Australian Decision Impact Study: the impact of Oncotype DX Recurrence Score (RS) on adjuvant treatment decisions in hormone receptor positive (HR+), node negative and node positive (N+9 early breast cancer (ESBC) in the multidisciplinary clinic. Poster presented at the 34th Annual CTREC-AACR San Antonio Breast Cancer Symposium, December 6-10, 2011. *Cancer Res* 2011; 71(suppl 3): abstract P4-09-18.